Discussion Paper

Title	**Hemostatic Medical Devices for Trauma Use**
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Hemostatic Medical Devices for Trauma Use

Introduction:

FDA is issuing this discussion paper to obtain feedback on ways to address the challenges related to the design, development, and evaluation of hemostatic medical devices. Specifically, the focus will be on the current challenges and opportunities with hemostatic medical devices for use in emergent situations due to injury.

This discussion paper is being released as part of the preparation for an FDA Public Workshop being held at the White Oak Campus, Maryland, September 3rd – 4th, 2014.

This discussion paper provides a brief overview of current unmet trauma care needs, currently available hemostatic products, challenges with the development and evaluation of hemostatic devices, and efforts to facilitate the development and review of these devices of obvious public health importance. It is important to note that the information contained in this document is not meant to convey FDA's views; rather, the information is provided to offer background information and the basis for discussions at the Public Workshop.

Section 1: Unmet Trauma Care Needs

The nature of traumatic injuries allows for very little time to perform life-saving interventions, and there are currently few options for treating life-threatening, non-compressible abdominal and junctional/inguinal hemorrhage. Consequently, hemorrhage remains a leading cause of death in both the civilian and military settings. Specifically, hemorrhage is responsible for 50-80% of combat casualty deaths [Ref: 1, 2, 3] and is the second leading cause of death in civilian trauma [Ref: 4]. Even when death is avoided, substantial blood loss is often associated with significant morbidities, including hypothermia, coagulopathy, impaired resuscitation, and acidosis. The severity of these problems correlates with the amount of total blood loss [Ref: 4, 5]. Hemorrhage may also lead to delayed mortality resulting from sepsis and multiple organ failure [Ref: 4, 5]. Thus, it is clear that early hemorrhage control is critical and that there is a need for hemostatic agents to save lives and reduce suffering.

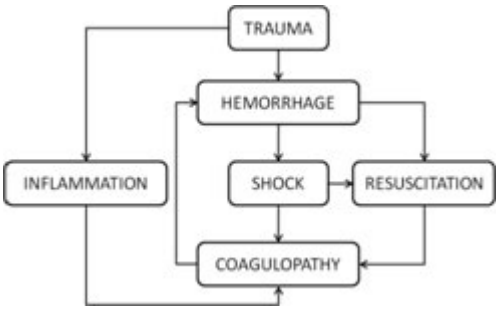

Figure 1. Association of trauma, hemorrhage, and related morbidities [Ref: 5].

Traumatic injuries in the military setting are especially difficult, with the majority of deaths occurring before reaching a medical treatment facility (MTF)[Ref: 6] and with the lack of adequate hemorrhage control at point-of-injury being the leading cause of potentially survivable (PS) deaths [Ref: 3, 7, 8, 9]. Based on a recent analysis of combat casualty data from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), Eastridge *et al* report that "in the cohort of casualties with PS wounds, the majority of mortality was associated with hemorrhage (90.9%)," with 67.3% of the hemorrhage being truncal, 19.2% junctional, and 13.5% extremity" (Figure 2) [Ref: 9].

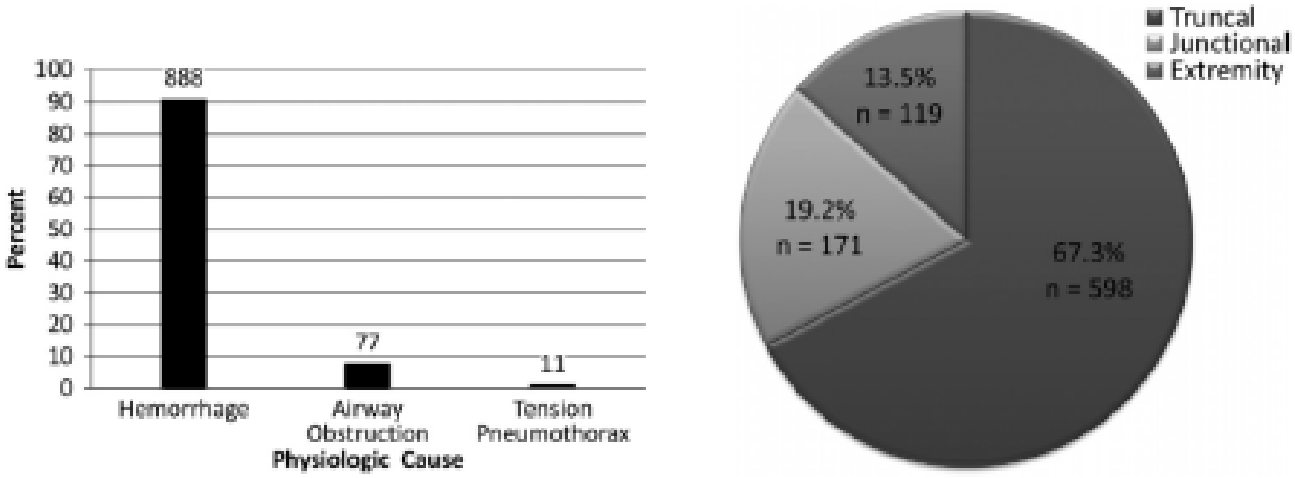

Figure 2. Physiologic focus of PS casualties from OIF and OEF, demonstrating that >90% of PS casualties were due to inadequate hemorrhage control [Ref: 9].

Eastridge *et al* note that within the past decade, a tremendous amount of evidence has been amassed validating improvements in combat casualty care once a casualty has reached an MTF but that no studies have comprehensively evaluated the outcomes of wounded warriors who died of their injuries before reaching an MTF. Based on their analysis, Eastridge *et al* conclude that during OIF and OEF, "there was no effective means to control or temporize junctional or truncal

sources of hemorrhage in the battlefield" [Ref: 4]. Notably, current Tactical Combat Casualty Care (TCCC) Guidelines provide no direct treatment for non-compressible hemorrhage [Ref: 10, 11]. The data collected from OEF and OIF and the lack of guidelines for treatment of non-compressible hemorrhage signify a clear need for an effective point-of-care treatment that will enable survival until arrival at an MTF.

Traumatic injuries and resulting hemorrhage are also challenging in the civilian setting. According to the National Trauma Institute, trauma is the leading cause of death for Americans between 1 and 44 years of age and the third leading cause of death overall. After a traumatic injury, hemorrhage is responsible for over 35% of pre-hospital deaths and at least half of traumatic deaths within 24 hours of hospitalization, many of which are potentially preventable [Ref: 5, 12]. While lessons learned from the military management of life-threatening external hemorrhage are beginning to be adopted in the civilian community, the use of tourniquets and hemostatic agents in the civilian EMS community is not widespread, though there is increasing interest in their use [Ref: 13].

The ideal hemostatic agent for combat casualty care and civilian trauma alike would have the following attributes [Ref: 14, 15]:

- FDA approved/cleared
- Stop severe arterial, venous, and soft tissue bleeding in < 2 min
- Maintain hemostasis for at least 2 hours
- Ready to use and easy to apply
- Require minimal training
- Be lightweight and durable
- Cause no harmful effect
- Have long shelf life (> 2 years).
- Stable in extreme environment for weeks
- Cost effective
- Biodegradable and absorbable (Truncal wound)

While the characteristics of an ideal hemostatic agent for both military and civilian use may be similar, the differences between the civilian and military populations may be significant, and the translation of military, battlefield experience to civilian trauma practice is unclear [Ref: 16]. In order to effectively integrate any future solutions for the treatment of non-compressible hemorrhage into both military and civilian trauma practice, dialogue among military and civilian practitioners involved in trauma care will be necessary for refining treatments by sharing experiences and providing constructive feedback.

Section 2: Overview of Available Products

There exists a large variety of hemostatic medical products on the market and in development to control potentially life-threatening bleeding in emergency situations when there may be no immediate medical facility nearby. There are several FDA premarket approval pathways for these hemostatic medical products, depending on whether the product is a drug, biologic, or device. This paper will focus on hemostatic medical devices regulated in FDA's Center for Devices and Radiologic Health (CDRH), though brief summaries of hemostatic medical products regulated in FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) are also included below.

FDA's CDRH classifies all medical devices based on the risks associated with the device. Devices are classified into one of three categories: Class I, Class II, and Class III. Class I devices are deemed to be low-risk and are therefore subject to the least regulatory controls. Class II devices are moderate risk devices, and Class III devices are generally the highest risk devices and are therefore subject to the highest level of regulatory control.

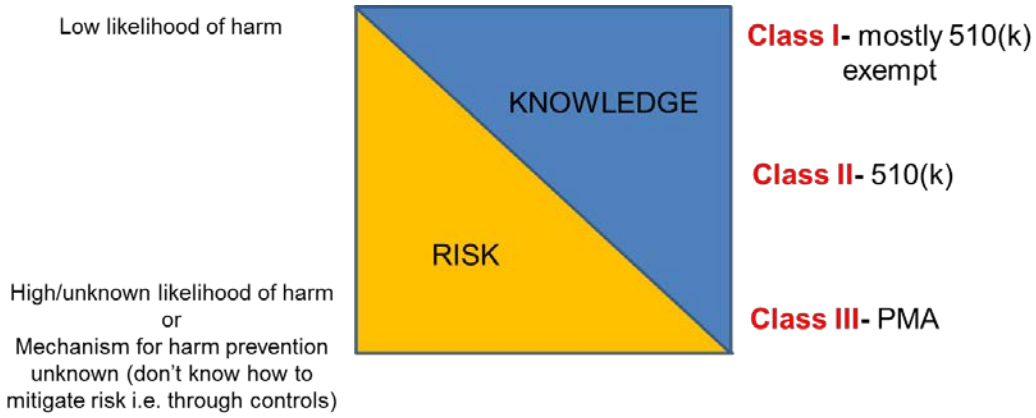

Figure 3. Medical device classification: Regulatory path determined using a risk-based approach.

For more information regarding the principal factors FDA considers when making benefit-risk determinations during the premarket review process for certain medical devices, please see FDA's Guidance for Industry and Food and Drug Administration Staff: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf).

Regulatory pathways used for medical devices include the premarket notification (510(k) clearance), Premarket Approval Application (PMA), and *de novo* classification process. A PMA is an application for approval for most Class III medical devices; the Sponsor must show reasonable assurance of medical device safety and effectiveness. The 510(k) clearance process typically applies to medical devices that are "substantially equivalent" to a Class I or II device already on the market. FDA has exempted almost all Class I and a few Class II devices from the premarket notification requirement (subject to the limitations on exemptions), though general controls [e.g., compliance with good manufacturing practices (GMP), prescription use restriction, general labeling, etc.] still apply. The *de novo* classification process provides a pathway to Class I or Class II classification for medical devices for which general controls or general and special controls (e.g., performance standards, post-market surveillance, special labeling requirements, guidelines, etc.) provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device.

Hemostatic devices regulated in CDRH include products such as Class I exempt tourniquets and gauze, various Class II devices (e.g., vascular shunts and junctional tourniquets classified as externally-applied vascular clamps), unclassified products (e.g., hemostatic wound dressings), Class III absorbable hemostatic agents (e.g., absorbable collagen, gelatin, regenerated cellulose, and polysaccharides), and those that may be proposed for other regulatory pathways, such as *de novo* petitions. Of the above-cited medical devices, only externally-applied vascular clamps and non-absorbable, expandable hemostatic sponge for temporary internal use devices fall into the category that is the focus of this workshop. These hemostatic medical devices are specifically indicated for the treatment of non-compressible junctional bleeding. The other medical devices, while for treatment of bleeding, are either not indicated for use in non-compressible traumatic hemorrhage or used in operative settings.

FDA's other Centers (i.e., CBER and CDER) also regulate hemostatic products. Approval pathways include the Biologics License Application (BLA) for biologics and New Drug Application (NDA) for drugs.

Hemostatic products regulated by CBER include fibrin sealants composed of purified, virus-inactivated/removed human fibrinogen and human or bovine thrombin, with or without added components such as virus-inactivated/removed human factor XIII and/or aprotinin. Such biologic products are licensed for use as adjuncts to hemostasis in patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. Products containing only thrombin (human, recombinant or bovine derived) are also licensed in the US as adjuncts to hemostasis during surgery.

Hemostatic products regulated by CDER include antifibrinolytic agents for use in enhancing hemostasis when fibrinolysis contributes to bleeding. The fibrinolysis-inhibitory effects are

through the inhibition of plasminogen activation. Fibrinolytic bleeding can be associated with life-threatening bleeding, surgical complications, hematological disorders, hepatic cirrhosis, or bleeding associated with certain malignancies. Urinary fibrinolysis can frequently be associated with life-threatening complications following severe trauma, anoxia, and shock. Some large trials have shown a use for antifibrinolytics in reducing the overall risk of death or death due to bleeding following trauma, while others have found no substantial difference in the receipt of blood transfusions between those that receive antifibrinolytics and placebo and unclear evidence of benefit in this setting.

Section 3: Current Challenges in the Evaluation of Hemostatic Medical Devices

Among other factors, investigational medical devices are assessed for a reasonable assurance of safety and effectiveness by weighing any probable benefit to health from the use of the medical device against any probable risk of injury or illness from such use. Methods to assess risk are important to this assessment. Evaluation of investigational devices for hemostasis presents scientific and clinical challenges that include the lack of validated bleeding severity definitions and bleeding severity assessment scales. Further, interspecies differences in coagulation challenge extrapolation of results associated with investigational device use since the correlation between animal models and human subjects is unknown.

In addition, there are several variables affecting hemorrhage severity and diagnosis that pose challenges in hemostatic device development and performance assessment, especially when human clinical data are difficult to obtain. In general, bleeding may be local or systemic, into an open or closed space, whether or not associated with any coagulopathy, e.g., due to anti-platelet agents such aspirin, NSAIDS, and clopidogrel, anti-coagulants such as heparin and warfarin, infection, inflammation (Disseminated Intravascular Coagulation), genetic disease, hemodilution, hypothermia, or the recently recognized 'trauma-induced coagulopathy.' Lack of methods to characterize risk of bleeding due to coagulopathy, the severity of bleeding at a local site, and the improvement in hemostasis with medical device intervention confounds an assessment of the investigational medical device benefit-risk.

Bleeding Severity Scale

Analogous to drugs, which may be expected to be systemically administered and active, hemostatic medical devices are expected to act locally at the bleeding site, i.e., to absorb free blood and create a mechanical barrier that simulates clot and prevents further egress of blood from an injured vessel. Recognition of the presence and distribution of bleeding sites and valid assessment of the severity of bleeding are necessary to optimize hemostatic device use and patient outcomes.

Considering the etiology of bleeding, bleeding severity scales and assessment methods have been developed for various specific scenarios [Table 1]. Such scales, however, assess patient status based upon clinical changes due to blood loss that is cumulative to the time of assessment and do not represent events at a specific bleeding site. Depending upon the cumulative blood loss and a patient's response and threshold for change in clinical markers, systemic signs and symptoms may lag behind local events.

Table 1: Bleeding Severity Scales and Assessment Methods

Bleeding Severity Scale/Assessment Method	**Description**
World Health Organization (WHO)	Standardized grading scale to measure the severity of bleeding [Ref: 17]
Vicenza bleeding score and its pediatric counterpart, the Pediatric Bleeding Questionnaire	Developed for patients with Von Willebrand's Disease [Ref: 18]
Thrombolysis in Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) and Bleeding Score	Used in antiplatelet therapy studies [Ref: 19]
The American College of Surgeons' Advanced Trauma Life Support shock classification	Correlates estimated total body blood loss with a patient's systemic parameters such as heart rate, blood pressure, neurologic status, and urinary output. This classification is based upon the systemic blood loss and expected signs and symptoms due to such loss.
The ABC (assessment of blood consumption) score	Has been reported to be practical for life-threatening bleeding in the field. For example, on the ABC scale, a penetrating injury with heart rate ≥ 120 or systolic blood pressure ≤ 90 is given a score of 2, and scores of 2 or more were likely to require massive transfusion ($\geq$10 units of PRBCs) in the ABC Score studies [Ref: 20]

Considerations for developing a localized bleeding severity scale include, among other factors:

- **Standard and clinically meaningful terminology and definitions** – e.g., for concepts including bleeding severity categories (scores), distinction between internal versus external bleeding, adjunct treatment, etc.
- **Varying product attributes** – e.g., product composition, intended use / indication for use, absorbable versus non-absorbable, implanted versus non-implanted, etc.

- **Scale robustness** – i.e., is it possible to use the same scale in all situations, such as for internal/external bleeding, compressible/non-compressible wounds, etc.?
- **Methods of validation** – i.e., what does it mean to validate?

Bench and Animal Models

In addition to challenges related to the lack of validated bleeding severity definitions and validated methods for measuring bleeding severity, ethical considerations related to performing human clinical studies under emergency use (e.g., difficulty obtaining informed consent) make it difficult to obtain pre-market clinical data for hemostatic devices. Consequently, bench, animal, and post-market data are important for assessing device safety and effectiveness and informing regulatory decisions. The challenge related to evaluating innovative hemostatic products is the translatability of animal model testing results to human clinical device use. For example, interspecies differences in coagulation are recognized and result in challenges in the interpretation of results, as well as correlation between models and extrapolation to clinical use [Ref: 21].

Due to the challenges associated with obtaining pre-market clinical data and translatability of current pre-clinical models, there is a clear need for the development of predictive models for assessing hemostatic devices. Predictive hemorrhage models would ideally include the following characteristics [Ref: 22]:

Ideal Compressible Hemorrhage Model

- Consistent Injury with reproducible bleeding outcomes
- High volume blood loss (measurable as the primary end point)
- 80-90% lethal without treatment
- Not treatable with regular gauze
- Mimics extremity or junctional injury
- Compatible with small volume hypotensive resuscitation principle
- Direct correlation between blood loss and mortality

Ideal Non-compressible Hemorrhage Model

- Intracavitary injury with severe bleeding outcomes
- High hemorrhage volume that can easily be measured (the primary end point)
- 70-90% lethal without hemostatic intervention
- No access for topical hemostatic treatment
- Compatible with small volume hypotensive resuscitation principle
- Direct correlation between blood loss and mortality

Such studies may evaluate primary endpoints such as blood loss volume, survival time, and percent survival and secondary endpoints including mean arterial blood pressure, time to hemostasis, hematocrit and platelet counts, and standard coagulation (PT, aPTT, fibrinogen).

While challenges related to the evaluation of hemostatic devices in the pre-market setting persist, post-market data will continue to be a valuable tool to assess safety and effectiveness of hemostatic products.

Section 4: CDRH post-market surveillance & Data Registries

Clinical data can be difficult to obtain for hemostatic medical devices being used in emergency in trauma situations. Therefore, it may not be practical to obtain large amounts of clinical testing data prior to clearance or approval of these hemostatic medical devices. FDA believes there may be opportunities to collect post-market data to gain additional understanding about certain benefits or risks of a device. For example, post-market data may be used to improve device labeling or to better-define target patient populations. The right balance of pre-market and post-market data collection can facilitate timely patient access to important new technology without undermining patient safety.

The use of existing registries [Table 2] to collect data on trauma patients may be a useful tool to expand the knowledge base regarding the use and performance associated with legally marketed hemostatic medical devices used in emergent situations. Database mining presents the potential to obtain retrospective analyses on hemostatic medical device performance to fill pre-market needs with regards to e.g., methods of clinical care and performance goals.

FDA is also expanding its capabilities for data analysis, and has the ability to perform complex analyses on large data sets using supercomputing resources.

Table 2: Existing Registries Collecting Data on Trauma Patients

Database	Description
Department of Defense (DoD) Trauma Registry	An extensive data repository that is updated weekly for DoD trauma-related injuries
Joint Trauma System http://www.usaisr.amedd.army.mil/joint_trauma_system.html	Concurrently collects and analyzes the data maintained in the DoD Trauma Registry in order to improve trauma care delivery and patient outcomes across the continuum of care, including point of injury, pre-hospital, patient movement, and acute, subacute, and chronic medical treatment facility care.
National Trauma Data Bank (NTDB)	NTDB serves the civilian sector. It is the largest aggregation of trauma registry data. These data are compiled annually and

https://www.facs.org/quality-programs/trauma/ntdb	disseminated in the forms of hospital benchmark reports, data quality reports, and research data sets.

Section 5: Summary of Questions/Challenges:

In summary, we are currently faced with the following questions and challenges related to the design, development, and evaluation of hemostatic medical devices:

- The lack of standardized definitions of bleeding severity and methods for validating bleeding severity scales used in the evaluation of hemostatic devices.

- What pre-clinical studies can be used to collect data when clinical data are difficult to obtain? What value do these models provide and what are their shortcomings?

- What options exist for obtaining clinical data for products used for emergency treatment of bleeding in both civilian and military settings, and which devices should be supported by clinical data?

- Novel product development to address unmet hemostatic trauma care needs in both the military and civilian setting. How can we address the differences between the civilian and military populations? To what extent can military experience translate to civilian trauma practice? What are anticipated training needs for this translation?

- Products used for emergency treatment of bleeding are often used by a variety of end users and in a variety of high-stress situations; improper or unnecessary device use has the potential to cause serious harm. What human factors issues exist with use of these products and how should these issues be studied (e.g., potential need for training and certification for use)?

- What are the implications of labeling for "military use only," and what criteria should be used for expanding military use only more broadly to civilian use?

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